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Evaluation of the use and efficacy of prothrombin complex concentrates in patients presenting to the emergency department with warfarin-induced hemorrhage

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ABSTRACT

Aims: Warfarin administration has been the standard treatment for many years to prevent thromboembolism in patients with prosthetic heart valves with atrial fibrillation. Because of warfarin`s narrow therapeutic window, and life-threatening bleeding, it is generally considered that this requires rapid and complete warfarin reversal. Although there are treatments such as vitamin K and fresh frozen plasma (FFP) to reverse the effects of warfarin, the most effective method involves using prothrombin complex concentrates (PCC). This study aims to evaluate the use and efficacy of PCC in patients with warfarin-induced bleeding in the emergency department.

Methods: The patients receiving PCC for warfarin reversal in the emergency department between January 1, 2019 – April 1, 2021, were identified from the hospital's electronic database. Demographic data, reasons for warfarin use, PCC indications, international normalized ratio (INR) values before and after PCC, and mortality of the patients were evaluated. The four-factor PCC dose was determined according to the patient's weight, admission, and target INR level.

Results: The mean age of the patients was 69.3±15.5 years. The female/male ratio was 1/1.5. The most common PCC indications were gastrointestinal bleeding (32.9%), urogenital bleeding (23.3%), epistaxis (12.3%), and urgent surgical need (12.3%). The median INR values pre- and post-treatment were 9.2 (range 2.1-11.8) and 1.8 (range 1.0-4.6). The mean dose of PCC was 1500 IU (min-max 750-3250 IU). In addition to PCC, all patients received vitamin K; 17.8% of the patients received erythrocyte suspension, and 10.9% of the patients received FFP. There were no PCC-related complications in the emergency department. After visiting the emergency department, 56.2% of the patients were discharged following successful treatment, 38.4% were admitted to inpatient services, and 5.5% were referred to an external center. 26% of the patients were followed in the intensive care unit (ICU). It is important to note that there were no fatalities in the emergency department. However, the mortality rate during the hospital stay was 5.5%.

Conclusion: Four-factor prothrombin complex concentrate (PCC) has been proven to be a safe and effective treatment for reversing bleeding caused by warfarin.

Keywords: Warfarin-associated bleeding, prothrombin complex concentrates, emergency department

INTRODUCTION

Warfarin is used as anticoagulant therapy in many thrombotic processes, such as pulmonary embolism, deep vein thromboembolism (DVT), and atrial fibrillation (AF). Warfarin-like vitamin K antagonists (VKA) inhibit vitamin K-dependent epoxide reductase, preventing the conversion of vitamin K-dependent clotting factors into their active forms.[1]

The most important side effect associated with warfarin is bleeding, and the risk of bleeding increases as a result of the increase in international normalized ratio (INR) values. Warfarin-induced bleeding is of concern due to the narrow therapeutic range and interindividual dose variability.[2] The first places of admission of patients with warfarin-associated

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bleeding are to the emergency services. Therefore, the rapid diagnosis and treatment of warfarin-associated bleeding by emergency physicians are essential. It is recommended to discontinue the use of VKAs, vitamin K, Fresh Frozen Plasma (FFP), or Prothrombin complex concentrate (PCC) to treat bleeding associated with warfarin.[3,4] Several studies have compared the effectiveness of FFP and PCC in treating warfarin-induced bleeding.[5,6] Emergency departments are the most important places of admission for patients with warfarin-related bleeding. Therefore, rapid diagnosis and treatment of warfarin-related bleeding by emergency physicians are gaining importance.

This study aims to determine the acute bleeding conditions due to warfarin, the treatment protocols, and the treatment results applied to the emergency department.

METHODS

The study was conducted with the approval of Samsun University Samsun Training and Research Hospital Clinical Researches Ethics Committee (Date:22.09.2021, Decision No:2021/6/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective and descriptive study included patients who applied to third level emergency department between January 2019 and April 2021, were older than 18 years of age, actively receiving warfarin treatment, had an INR level above 2, had active bleeding, or were using active warfarin but did not have active bleeding but required emergency surgical intervention and received PCC treatment. Patients under 18 years of age, patients who did not use warfarin, and patients with an INR level below were excluded from the study.

Sociodemographic data such as age and gender, indications for warfarin use, vital signs, comorbid diseases, bleeding characteristics (major bleeding characteristics are defined as GI bleeding, urogenital bleeding, urgent surgical need, and hemoptysis, intracranial bleeding), and laboratory data were analyzed from the patients in the study's electronic records. Bleeding parameters before and after the treatment were compared. All patients included in the study were followed up for 1 month for thromboembolic events. The outcome characteristics (mortality and adverse thromboembolic events) of the patients were also recorded. All patients included in the study received vitamin K. Other therapies (vitamin K, FFP) recommended to patients other than PCC were recorded in the emergency department. 20 minutes after PCC treatment, whether the patients reached target INR values was analyzed.

The online calculation table developed by the manufacturer was used so that the PCC doses were based on the patient's weight, the INR values at admission, and the target INR values, with the target INR<2.1.[7]

Statistical analyses were performed using the SPSS version 21.0 (Chicago, USA) software. The suitability of the variables for normal distribution was examined using visual (histogram and probability graphs) and analytical methods (*Kolmogorov Smirnov, Shapiro-Wilk test*). Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data, median in non-normally distributed numerical data, and number and percentage in nominal data. Customarily distributed numerical variables between the two groups were analyzed *using the "t-test in independent groups"*. Non-normally distributed numerical variables were analyzed using the *"Mann Whitney U test"* between two independent groups and the *"Wilcoxon signed rank test"* between two dependent groups. " *Chi-square analysis"* was used to compare the nominal data. "*Spearman test"* was used in correlation analysis. In the statistical analyses in the study, values below $p<0.05$ were considered statistically significant.

RESULTS

73 patients were included in the study and 29 (39.3%) of these patients were female and 44 of the patients were male (60.7%). The mean age of the patients was 69.3±15.5 years. The most common indications for warfarin therapy were dysrhythmia (47.9%), heart valve prosthesis (32.9%), and embolism/thrombosis (8.2%). The most common reasons for presentation to the emergency department were GI bleeding (32.9%), followed by urogenital bleeding (23.3%), epistaxis (12.3%), and urgent surgical need (12.3%). The sociodemographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of the patients in the study

Characteristics		n (%)
	Age (year) (mean ± SD)	69.3±15.5
Gender	Female	29 (39.7)
	Male	44 (60.3)
Bleeding type	Major bleeding	32 (43.8)
	Minor bleeding + Supratherapeutic INR	41 (56.2)
Presenting complaint	GI bleeding	24 (32.9)
	Urogenital bleeding	17 (23.3)
	Epistaxis	9 (12.3)
	Urgent surgical need	9 (12.3)
	Subcutaneous hemorrhage	5 (6.8)
	Hemoptysis	4 (5.5)
	Intracranial hemorrhage	3 (4.1)
	Hemarthrosis	1 (1.4)
	Conjunctival hemorrhage	1 (1.4)
Indication for the Warfarin usage	Dysrhythmia	35 (47.9)
	Prosthetic heart valve	24 (32.9)
	History of embolism/thrombose	6 (8.2)
	Peripheral arterial disease	5 (6.8)
	Stroke	2 (2.7)
	Pulmoner embolism	1 (1.4)

SD: Standard deviation, INR: International normalized ratio, GI: Gastrointestinal.After PCC treatment, 75.3% (n=55) of the patients had reached to target INR range, while 24.7% (n=18) were unable to reach to the target INR range. While 56.2% of the patients were discharged after treatment from the emergency department, 38.4% were hospitalized in the relevant wards. In addition, 26% of the patients were hospitalized in intensive care units. During the follow-up in the emergency department, no mortality occurred in

any patient, while mortality occurred in 5.5% (n=4) of the hospitalized patients. The length of stay in the emergency department was 4 (2-28) hours, and after PCC treatment there were observed no thromboembolic complications for one month.

INR, PT, aPTT, Hb, and Htc values of the patients at the admission to the emergency department and after PCC treatment are presented in Table 2. Accordingly, INR, PT and aPTT levels decreased significantly after PCC treatment (p<0.001).

Table 2. Analysis of laboratory parameters at the time of admission to the emergency department and after PCC treatment

Parameter	Admission Med (min-max)	After PCC Med (min-max)	p-value
INR	9.2 (2.1-11.8)	1.8 (1-4.6)	<0.001*
PT (sec)	96.5 (9.5-121)	20.4 (11.2-159)	<0.001*
APTT (sec)	72.6 (28.5-190)	32.8 (12-90)	<0.001*
Hb (g/dL)	11 (4.5-17.0)	10.5 (5.2-15)	0.011*

INR: International normalized ratio, PT: Prothrombin time, APTT: Activated partial thromboplastin time, Hb: Hemoglobin, PCC: Prothrombin Complex Concentrates
*Wilcoxon signed rank test was used in all analyzes.

Patients who achieved the target INR value with PCC treatment were compared to those who did not. It was found that patients who achieved the target INR value had shorter lengths of stay in the emergency department (p=0.035). Patients who did not achieve the target INR value had a higher prevalence of arrhythmia (p=0.027) and multiple comorbidities (p=0.022) Table 3.

Table 3. Comparison of patients, who reached and failed to reach the target INR level after PCC treatment

Characteristics			Target INR to the value of those who reach (n=55;%75.3)	Target INR to the value of those who can't reach (n=18; %24.7)	p value
Multiple comorbidity (+)		n (%)	17 (30.9)	11 (61.1)	0.022**
Laboratory	INR	Med (min-max)	8.7 (2.1-11.8)	9.9 (5.4-11.0)	0.072*
	Pt (sec)	Med (min-max)	92.1 (9.5-121)	106 (59.3-120)	0.116*
	Aptt (sec)	Med (min-max)	78.7 (28.5-190)	68.4 (39.3-190)	0.828*
	Hb (g/dl)	Med (min-max)	11.2 (4.5-15)	10.5 (6.1-17)	0.217*
	Plt (103/µL)	Med (min-max)	227 (98-662)	235 (82-479)	0.828*
	Urea (mg/dL)	Med (min-max)	48 (19-290)	93 (29-291)	0.004*
Mortality (+)		n (%)	4 (7.3)	0	
Length of stay in the emergency department (hours)		mean ± SD	7.8 ± 8.6	12.3 ± 11.3	0.035*

INR: International normalized ratio, PT: Prothrombin time, APTT: Activated partial thromboplastin time, Hb: Hemoglobin, PCC: Prothrombin complex concentrates, Plt: Platelet
*Mann-Whitney U test, **Chi-Square test

The analysis of patients admitted to the intensive care unit (ICU) and those not admitted is presented in Table 4. Patients received similar doses of PCC treatment in the emergency department (p=0.340). Patients hospitalized in the ICU had a higher frequency of major bleeding (p<0.001) and a longer length of stay in the emergency department (p=0.027). In addition, patients hospitalized in ICU had lower systolic blood pressure (p=0.049), Hb (<0.001), Htc (p<0.001) and higher urea values (p=0.008).

Correlation analyses of PCC dose and sociodemographic, clinical and laboratory outcomes are presented in Table 5. Accordingly, PCC dose was moderately positive correlated with INR (r=0.360; p=0.002), PT (r=0.310; p=0.008), aPTT (r=0.305; p=0.009) and PLT (r=0.323; p=0.005), while AST (r=0.249; p=0.035) and lower positive correlated with length of stay in the emergency department (r=0.260; p=0.029).

Table 4. Comparison of laboratory parameters and PCC treatment doses in patients admitted to intensive care unit and non-admitted patients

			ICU (+) (n=19)	ICU (-) (n=54)	p-value
Bleeding type	Major	Med (min-max)	16 (84.2)	16 (29.6)	<0.001**
	Minor+high INR value	Med (min-max)	3 (15.8)	38 (70.4)	
Vital parameters at the time of admission	SBP (mmHg)	mean ± SD	108 ± 30	124 ± 28	0.049***
	DBP (mmHg)	mean ± SD	67 ± 15	74 ± 14	0.061***
	Pulse	mean ± SD	100 ± 20	92 ± 19	0.129***
Laboratory	INR	Med (min-max)	9.6 (2.1-11)	9.2 (2.1-11.8)	0.915*
	Pt (sec)	Med (min-max)	102 (23-121)	96 (9-120)	0.469*
	Aptt (sec)	Med (min-max)	71 (32-190)	73 (28-190)	0.806*
	Hb (g/dL)	Med (min-max)	7.8 (4.5-14)	11.5 (5.5-17)	<0.001*
	Htc (%)	Med (min-max)	23 (13.1-42)	34.1 (16.5-46)	<0.001*
	Plt (103/µL)	Med (min-max)	230 (114-535)	227 (82-662)	0.980*
	Urea (mg/dL	Med (min-max)	74 (32-291)	45 (19-290)	0.008*
	Cr (mg/dL)	Med (min-max)	1.0 (0.7-4.5)	1.0 (0.5-6.4)	0.850*
PCC (IU) Med (min-max)		Med (min-max)	1500 (750-3000)	1500 (750-3250)	0.340*
Length of stay in the emergency department (hours)		mean ± SD	14.7±14.0	6.8±6.1	0.027*

PCC: Prothrombin complex Concentrates, ICU: Intensive care unit, INR: International normalized ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PT: prothrombin time, APTT: Activated partial thromboplastin time, Hb: Hemoglobin, Htc: Hematocrit
*Mann-whitney u test, ** Chi-square test, *** Independent sample t test, Min: Minimum, Max: Maximum

Table 5. Correlation analyses of PCC dose and sociodemographic, clinical, and laboratory outcomes

		PCC dose	
		Correlation rate (r)	p-value
Age		0.005	0.968
Comorbidity numbers		0.043	0.719
Values at the time of admission	SBP	-0.049	0.682
	DBP	0.017	0.884
	Pulse	0.191	0.105
	INR	0.360	0.002
	PT	0.310	0.008
	aPTT	0.305	0.009
	Hb	-0.062	0.605
	Htc	-0.077	0.516
	PLT	0.323	0.005
	AST	0.249	0.035
	ALT	0.128	0.283
Length of stay in the emergency department		0.260	0.029
Length of stay in the ICU		0.425	0.070
Length of stay in the services		0.076	0.765

PCC: Prothrombin complex concentrates, ICU: Intensive care unit, INR: International normalized ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PT: Prothrombin time, APTT: Activated partial thromboplastin time, Hb: Hemoglobin, Htc: Hematocrit, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase
* Spearman rank correlation test was used in all analyses.

DISCUSSION

Warfarin is a vitamin K antagonist used for the primary and secondary prevention of arterial and venous thromboembolism in prosthetic heart valves, atrial fibrillation, peripheral arterial disease, antiphospholipid syndrome, and recurrent myocardial or cerebral infarcts. The critical challenge in warfarin therapy lies in maintaining a delicate balance between anticoagulation and the risk of bleeding. The narrow therapeutic range, high food-drug interactions, and different dose requirements according to the patient increase the risk of bleeding in patients using warfarin. In addition to methods such as vitamin K, FFP, and erythrocyte suspension replacement, PCC is significant among the treatment options for warfarin-related bleeding.[8] Especially compared with FFP, PCC has been reported to benefit patients more effectively in a shorter time frame, with less volume load and less risk of infection.[5,6] Perhaps the most crucial disadvantage of PCCs is that they are more expensive than other treatments.

In this study, in which we aimed to investigate the efficacy of PCC use in patients presenting to the emergency department with symptoms and signs of warfarin-induced bleeding, we found that PCC treatment significantly decreased INR levels. Similar to our study, Majeed et al.[9] evaluated patients who presented to the emergency department with warfarin-induced bleeding and received PCC treatment. In this study, the INR value of the patients was found to be 1.7 after PCC transfusion, and it was reported that target INR values were reached in 56.9% of the patients. It was also found that mortality developed in 10% of the patients. In our study, the target INR level was reached in 75.3% of the patients, and our mortality rate was 5.5%. The higher number of patients with intracranial hemorrhage in this study by Majeed et al.[9] compared to our study may explain the difference in mortality rates. Reactions developing after PCC transfusion may also contribute to this situation. Indeed, the analysis above reported that 3.8% of patients developed thromboembolic events after PCC. Still, no thromboembolic event was observed during the follow-up of the patients in our study.

Different results on reaching target INR levels after PCC treatment have been obtained from other studies. In the study by Appleby et al.[10], the INR value was reduced below 1.5 in 88.2% of patients after PCC. The fact that the INR values of the patients at the time of presentation were lower (median 4.3) compared to our study and that only 17 patients were included in the study may have been effective in reporting a higher success rate. Pabinger et al.[11] said that target INR values were achieved in 93% of 43 patients after PCC treatment. Although considerably higher than our study, the median INR value at admission was 3.2 in this study, which may have led to high rates.

In our study, while no mortality was observed in the emergency department in patients who underwent PCC due to warfarin-related bleeding, the mortality rate in inpatient services (ward/intensive care unit) was found to be 5.5%. The reason for this may be the short follow-up time of the patients in the emergency department and transfer to inpatient services after initial treatment, early recognition of bleeding, and rapid intervention. Studies are reporting similar and higher mortality rates to our study.[12] Karaca et al.[13] said that mortality developed in 5% of 20 patients treated with PCC. In this study, similar to our study, 40% of the patients were discharged after treatment in the emergency department, 40% were consulted at the relevant branch, and 15% were hospitalized in the ICU.

In our study, patients who failed to reach the target INR level in the emergency department had more than one comorbid disease, and their stay in the emergency department was longer. This may have been due to the prolonged consultation process in the emergency department. Our findings indicate that it is more challenging to return to the target INR level due to increased comorbidities. In addition, an increase in the number of comorbidities may have led to a rise in bleeding severity or difficulty in warfarin dose adjustment. In warfarin-related bleeding, the negative effect of the amount of bleeding on prognosis has been shown in previous studies.[14] It is thought that the rate of reaching the target INR range in treatment with PCC will be lower because coagulation factors will be lost more in patients with more bleeding. Therefore, early intervention in patients with significant bleeding may have a favorable effect on prognosis. In our study, the correlation between high admission INR levels and PCC doses indirectly supported this.

PCCs show both faster and safer efficacy compared to FFP in reversing the effects of VKAs.[15] In studies using PCCs in treating warfarin-induced bleeding, PCCs were reported to be very safe and effective. [9,12,16] In 2017, Brekelmans et al.[17] evaluated the efficacy and safety of PCCs in the reversal of vitamin K antagonist effects in a meta-analysis in which a total of 19 studies and 3000 patients were assessed, and it was stated that PCCs had a shorter time to reach the target INR and lower mortality rates and complications. In conclusion, the meta-analysis reported that PCCs were safer and more effective than FFP.

Although the efficacy of PCCs in reversing the effect of warfarin has been proven, they are used in combination with other treatment modalities.[18] In our study, vitamin K was administered to all patients in the emergency department. In addition, erythrocyte suspension (17.8%) was issued in patients with severe bleeding. FFP was administered to 3 patients (4.1%) with high control INR values. Other studies have reported that other treatment modalities were used at different rates. In the study by Majeed et al.[9], vitamin K transfusion was administered in 74% of patients who underwent PCC, and FFP transfusion was administered in 34% of patients who underwent PCC. Access to PCC and other treatment modalities and different clinical presentations of the patients may have been adequate in the difference between the studies regarding other treatment frequencies.

Warfarin is an effective anticoagulant agent that is frequently preferred for the prevention of complications, including stroke, especially in atrial fibrillation.[19] In the study by Soyuncu et al.[12], in which the effect of warfarin was reversed with PCC, the most common indications for warfarin were

atrial fibrillation (49.4%), heart valve replacement (21%), pulmonary embolism (12%) and deep vein thrombosis (12%). In our study, the most common indications for warfarin were similarly dysrhythmia (47.9%), heart valve replacement (32.9%) and embolism (8.2%).

In our study, we found that PCC treatment was administered due to GI bleeding (32.9%), urogenital bleeding (23.3%), epistaxis (12.3%) and surgical requirement (12.3%). In the literature, indications for PCC are reported similar to our study, but different indications and rates have also been reported. In the study by Majeed et al.[9], the most common types of bleeding were reported as intracranial hemorrhage (37%), GI bleeding (13%) and intramuscular bleeding (4%), respectively. In the study by Soyuncu et al.[12], the most common causes of bleeding in patients undergoing PCC were GI bleeding (32%), respiratory system bleeding (22.6%), muscular bleeding (12%) and urinary bleeding (12%), respectively. Toth et al.[20] reported that the most common indications for PCC were emergency surgery (29.8%), GI bleeding (27.5%) and intracranial hemorrhage (26.7%), respectively.

Limitations

Our study had some limitations. The number of patients included in our study was relatively small. The effect of PCC was evaluated at 30 minutes in most studies. However, this period could not be standardized in our research because of the study's retrospective design. In addition, the effect of PCCs on mortality could not be evaluated clearly because of the small number of patients with mortality.

CONCLUSION

PCC significantly reduces INR values for the reversal of warfarin-induced anticoagulation in the emergency department. However, treatment may be inadequate due to existing comorbidities.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Samsun University Samsun Training and Research Hospital Clinical Researches Ethics Committee (Date:22.09.2021, Decision No:2021/6/8).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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